REMARKS

Claims 8, 10-14, and 18-43 were pending in the application. Claim 35 has been amended. Following entry of this Amendment and Response, claims 8, 10-14, and 18-43 will be pending in the instant application.

Support for the amendment to the claim 35 can be found throughout the specification and claims as originally filed. No new matter has been added.

The foregoing claim amendment should in no way be construed as acquiescence to any of the Examiner's rejections and was made *solely* to expedite prosecution of the present application. Applicants reserve the right to pursue the claims as originally filed or previously pending prior to entry of this Amendment and Response in a separate application(s).

Rejection of Claims 8, 10-14, 18-26, and 28-43 Under 35 U.S.C. § 103(a)

The rejection of claims 8, 10-14,18-26, and 28-43 under 35 U.S.C. § 103(a) as being obvious in view of Oh *et al.* (Journal of the American Academy of Dermatology, 42(5):829-830, 2000) in combination with Salfeld *et al.* ([a] WO 97/29131 or [b] U.S. Patent No. 6,509,015 B1), and Keystone *et al.* ("The Fully Human Anti-TNF Monoclonal Antibody, Adalimumab (D2E7), Dose Ranging Study: The 24-Week Clinical Results in Patients with Active RA on Methotrexate Therapy (The ARMADA Trial)," *Presented at the Annual Meeting of the European League Against Rheumatoid Arthritis (EULAR), Prague, Czech Republic,* June 2001) has been maintained. Applicants respectfully disagree and traverse the rejection.

Pending claims 35-42 are each directed to a method of treating *psoriasis* in a subject consisting of *subcutaneous* administration of a dosage consisting of *10-150 mg* of a *human anti-TNFα antibody, or an antigen-binding fragment thereof*, whereby the dosage of the antibody, or antigen binding portion thereof, *is the same dosage throughout the course of treatment.* Pending claim 43 requires a dosage of a *human anti-TNFα antibody, or an antigen-binding fragment thereof*, for the treatment of *psoriasis*, whereby the dosage of the antibody, or antigen binding portion thereof, *comprises 10-150 mg and is the same dosage throughout the course of treatment.* Each of pending claims 8, 10-14, and 18-34 is directed to a method of treating *psoriasis* in a subject comprising *biweekly, subcutaneous* administration of a dosage

of a *human anti-TNFα antibody, or an antigen-binding fragment thereof*, whereby the dosage of the antibody, or antigen binding portion thereof, *comprises 10-150 mg and is the same dosage throughout the course of biweekly treatment.*

Thus, each of the pending claims requires *subcutaneous administration* of a dosage of a *human anti-TNFα antibody, or an antigen-binding fragment thereof*, for the treatment of *psoriasis,* whereby the dosage of the antibody, or antigen binding portion thereof, *comprises 10-150 mg and is the same dosage throughout the course of treatment.* Claims 8, 10-14, and 18-34 further require *biweekly* administration of the antibody, or antigen binding portion thereof.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). MPEP 706.02(j).

The test for *prima facie* obviousness is consistent with the legal principles enunciated in *KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007). *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.,* 492 F.3d 1350, 1356 (Fed. Cir. 2007). As suggested by the Examiner, "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1397 (see page 7 of Office Action).

The Examiner has taken the position that the claimed invention would have been obvious to try based on the cited references (see MPEP § 2143 (E) and Office Action page 7). As described in MPEP § 2143 (E), to reject a claim based on this rationale, the Examiner must resolve the *Graham* factual inquiries, and subsequently establish a finding that at the time of the invention, there had been a recognized problem or need in the art; a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem; a finding that one

of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness based on the aforementioned rationale.

The primary reference relied upon by the Examiner is Oh *et al.*, which reports treatment of inflammatory bowel disease with an intravenous infusion of 5 mg/kg of infliximab. The patient described in Oh *et al.* also had recalcitrant severe psoriasis, which was improved after the infusion of infliximab.

Oh *et al.* does not teach or suggest subcutaneous administration of a human TNFα antibody, or antigen-binding portion thereof, at a dosage comprising 10-150 mg, where the dosage is the same dosage throughout the course of treatment. To make up for these deficiencies, the Examiner combines the teachings of Oh *et al.* with Salfeld *et al.* and Keystone *et al.* Salfeld *et al.* describes functional human TNFα antibodies, and Keystone describes results of a clinical trial for rheumatoid arthritis using D2E7, a human TNFα antibody. Applicants respectfully submit that the Examiner has failed to establish how one of ordinary skill would arrive at the claimed invention predictably and with an expectation of success given the teachings of the cited art.

The primary reference cited by the Examiner, Oh *et al.*, teaches "the first reported case of successful anti-TNF-α therapy in psoriasis" (see page 830, second column, second paragraph). The Examiner suggests that Oh *et al.* provides motivation to administer a human anti-TNFα antibody such as D2E7 "in view of the limited and short-term efficacy of infliximab" (see page 7 of Office Action). Applicants respectfully submit, however, that no such teaching can be found in Oh *et al.* Oh *et al.* describes the treatment with infliximab as "successful" and a "[d]ramatic improvement" (see abstract, first paragraph, and conclusion paragraph), and does not refer to the treatment as "short term" or "limited" in efficacy as characterized by the Examiner. As such, Applicants respectfully submit that the Examiner has failed to establish the recognized problem or need in the art raised by Oh *et al.*, as Oh *et al.* teaches *successful* treatment of psoriasis. Thus, the Examiner has failed to establish

how, at the time of the invention, there was a recognized problem in the art given the successful teachings of Oh *et al.*; therefore, a *prima facie* case of obviousness based on the first required element of the alleged "obvious to try" line of reasoning (MPEP § 2143 (E)) has not been satisfied.

Importantly, the Examiner seems to be taking contradictory positions regarding the teachings of Oh *et al.* The Examiner suggests that "one of ordinary skill in the art would have been motivated to administer the fully human D2E7 antibody or antigen-binding fragments thereof subcutaneously at 20 mg, 40 mg, or 80 mg every other week for the treatment of psoriasis in view of the limited and short-term efficacy of infliximab as taught by Oh *et al.*" The Examiner also suggests, however, that "one of ordinary skill in the art would have a reasonable expectation of success in view of the teachings of Oh *et al.* providing evidence that the administration of an anti-TNFα antibody is clinically effective for psoriasis." Thus, the Examiner relies upon Oh *et al.* for providing both motivation in that the reference allegedly teaches a need for better treatment of psoriasis ("in view of the limited and short-term efficacy of infliximab as taught by Oh *et al.*"), and for teaching a reasonable expectation of success ("in view of the teachings of Oh *et al.* providing evidence that the administration of an anti-TNFα antibody is clinically effective for psoriasis"). *Applicants respectfully submit that the Examiner is using the Oh et al. reference to support opposite positions.* It is not clear how a single reference can teach both a "clinically effective" treatment for psoriasis and "limited and short-term efficacy" for psoriasis given the same treatment.

Applicants respectfully submit that the Examiner has also failed to establish how the claimed methods were selected from a finite number of identified, predictable solutions, as required under the guidelines set forth under MPEP § 2143 (E) for establishing obviousness under the "obvious to try" rationale. Dosage amounts alone or in combination with a dosing schedule provide an infinite number of possible combinations for treatment. There exists a limitless number of dosage amounts that can be used in any given treatment, as there also exists a limitless dosing schedule in terms of how frequently an agent may be delivered. Accordingly, the combination of dose amounts and frequency is equally infinite.

The Examiner is of the opinion that one of ordinary skill would look to Keystone *et al.* (directed to rheumatoid arthritis treatment) for guidance regarding treatment of psoriasis because "one of ordinary skill in the art would have been motivated to at least administer the D2E7 antibody…subcutaneously at 20 mg, 40 mg, or 80 mg every other week for the treatment of psoriasis" given "the teachings of Keystone *et al.* [which] indicate that the administered D2E7 antibody was well tolerated and therapeutically effective." Applicants disagree and respectfully submit that one of ordinary skill in the art would not combine the teachings of Keystone *et al.* with Oh *et al.* to arrive at the claimed invention. As described above, Oh *et al.* teaches successful treatment of psoriasis. Thus, one of ordinary skill in the art would follow the teachings of Oh *et al.* regarding psoriasis treatment, rather than modify the treatment method described therein. In addition, the claimed methods are directed to dermatological disease, *i.e.,* psoriasis, whereas Keystone describes treatment of rheumatism, *i.e.,* rheumatoid arthritis. There is no evidence of record that it was conventional in the art to seek treatment methods from one disease state to another, *e.g.,* rheumatoid arthritis to psoriasis.

The pending claims require *subcutaneous administration* of a dosage of a human anti-TNFα antibody, or antigen-binding fragment thereof, wherein the dosage *comprises 10-150 mg and is the same dosage throughout the course of treatment*. Oh *et al.* teaches an *intravenous, weight-based dose* that is different than the *subcutaneous, fixed dose* of the claimed invention. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, . . . would be led in a direction divergent from the path that was taken by the applicant." *In re* Haruna, 249 F.3d 1327, 1335 (Fed. Cir. 2001) (quoting Tec Air, Znc. v. Denso Mfg. Mich. Znc., 192 F.3d 1353, 1360 (Fed. Cir. 1999)). Applicants submit that based on the *successful* teachings of Oh *et al.* regarding *intravenous* administration of infliximab using a *weight-based* dosing scheme, one of ordinary skill in the art would not be led to the claimed method of *subcutaneous* administration of a *fixed dose* (*i.e.,* the same dosage throughout the course of treatment). Even assuming *in arguendo* that one of ordinary skill would be motivated to substitute a human anti-TNFα antibody, or antigen-binding fragment thereof, for infliximab for treating psoriasis based on the teachings of Oh *et al.* (which Applicants deny), the Examiner has not supported why

one of ordinary skill would have changed the regimen described in Oh *et al.* Given the successful treatment described in Oh *et al.*, Applicants submit that one of ordinary skill would have logically followed the *intravenous* and *weight-based* dosing scheme described in Oh *et al.*

In addition, dosing amounts and schedule of administration for infliximab is *different* for rheumatoid arthritis and psoriasis. As described in Applicants' Response of November 3, 2008, the recommended dosage regimen for infliximab for the treatment of *psoriasis is 5 mg/kg at 0, 2 and 6 weeks followed by 5mg/kg every 8 weeks*, whereas the recommended dosage regimen of infliximab for *rheumatoid arthritis is 3 mg/kg at 0, 2 and 6 weeks followed by 3 mg/kg every 8 weeks*. Thus, one of ordinary skill in the art (assuming *in arguendo* that motivation even existed to administer a human anti-TNFα antibody, or antigen-binding portion thereof, for treating psoriasis) would *not* have had an expectation of success in applying the teachings of rheumatoid arthritis described in Keystone *et al.* to psoriasis. Furthermore, Salfeld *et al.* does not teach or suggest the claimed dosage comprising 10-150 mg which is the same dosage throughout the course of treatment, *but instead teaches weight-based dosing commensurate with the teachings of Oh et al.* (see page 33, last paragraph of Salfeld *et al.* which teaches a dose of 0.1-20 mg/kg). Applicants note that the *weight-based doses* of Oh *et al.* and Salfeld *et al.* are entirely different than the claimed *fixed body dose, i.e.,* dose that is the same throughout the course of treatment.

In view of the above, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 8, 10, 12, and 27 Under 35 U.S.C. § 103(a)

Claims 8, 10, 12 and 27 have now been rejected as being unpatentable over Oh *et al.* (Journal of the American Academy of Dermatology, 42(5):829-830, 2000) in view of Salfeld *et al.* ([a] WO 97/29131 and Keystone *et al.* ("The Fully Human Anti-TNF Monoclonal Antibody, Adalimumab (D2E7), Dose Ranging Study: The 24-Week Clinical Results in Patients with Active RA on Methotrexate Therapy (The ARMADA Trial)," *Presented at the Annual Meeting of the European League Against Rheumatoid Arthritis (EULAR), Prague, Czech Republic,* June 2001) and Neuner *et*

al. (Photochem. Photobiol 59(2):182, Feb. 1994) on the ground that it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to arrive at the claimed combination methods of treating psoriasis, in view of the combined teachings of these references. Applicants respectfully disagree and traverse the rejection.

As argued above, the Examiner has failed to establish a *prima facie* case of obviousness based on the combined teachings of Oh *et al.*, Salfeld *et al.*, and Keystone *et al.* While Neuner *et al.* describes PUVA therapy for treating psoriasis, the reference does not make up for the deficiencies described above with respect to the primary reference (Oh *et al*) and the secondary references (Salfeld *et al.* and Keystone *et al.*).

In the above rejection of claims 8, 10, 12 and 27, the Examiner states that Salfeld *et al.* teaches advantages of human antibodies and provides dosing ranges, which would provide motivation to combine Oh *et al.* with Salfeld *et al.* As stated above, the Examiner has provided no basis for a recognized problem or need in the art as set forth in the primary reference (Oh *et al.*). The teachings of Salfeld *et al.* with respect to the advantages of human antibodies do not establish that there was a recognized problem or need in the art with regarding chimeric antibodies, *e.g.*, infliximab, described in Oh *et al.* To this point, Applicants previously submitted the FDA-approved label for infliximab (to evidence various dosing schedules), which shows that chimeric antibodies are acceptable and approved forms of treatment.

With respect to the teachings of Salfeld *et al.* and methods for administering antibodies, the Examiner also cites to MPEP § 2144.05 II B to support the assertion that Salfeld *et al.* teaches that "the dosage regimen for anti-TNFα antibody, including dosing scheduling and amount, is a recognized results-effective variable." Applicants respectfully disagree with this comparison. MPEP § 2144.05 II B describes obviousness guidelines with respect to *optimization of ranges*, and suggests that "[a] particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result before a determination of the optimum or workable ranges of said variable *might be characterized* as routine experimentation" (emphasis added). Salfeld *et al.* describes general methods for administering antibodies, and describes an exemplary weight-based dosing range (as described

above) which is distinct from the claimed methods. Salfeld *et al.* provides general teachings directed to a dosage regimen distinct from the claimed methods, and describes a dose range which is not commensurate with the claimed invention as it is weight-based.

Accordingly, Applicants respectfully request that the rejection of the pending claims on the ground of obviousness be reconsidered and withdrawn.

Provisional Rejection of Claims for Non-Statutory Obviousness-Type Double Patenting

The rejection of claims 8, 10-14, 18-26, and 28-43 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-10, 16-21, 78-79, 81, 84, 86-88, 95, 97-98, and 100-104 of copending Application No. 10/163,657 in view of Oh *et al.* was maintained. The Examiner has also maintained the provisional rejection of claims 8, 10-14, 18-25, and 28-43 as being unpatentable in view of claims 5, 9-22, 25-26, and 28-53 of copending Application No. 11/104,117 in view of Oh *et al.* Furthermore, claims 8, 10-14 and 18-25 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claim 15 of copending Application No. 11/233,252 (allowed) in view of Oh *et al.* and Keystone *et al.*

Applicants note that these rejections are provisional in nature and respectfully submit that they will be further addressed when appropriate, *i.e.*, when the nonstatutory obviousness-type double patenting rejection is the only rejection remaining in the later-filed application (MPEP § 804 I.B.).

Rejection of Claims for Non-Statutory Obviousness-Type Double Patenting

Claims 8, 10-14, 18-25 and 28-43 and are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-7, 36-39 and 69-70 of U.S. Patent No. 6,509,015 B1, to Salfeld *et al.*, in view of Oh *et al.* and Keystone *et al.* Applicants respectfully disagree and traverse the rejection.

As argued above, the combined teachings of Salfeld *et al.*, Oh *et al.* and Keystone *et al.* fail to provide a reasonable expectation of success for the treatment of psoriasis with a subcutaneous dosage regimen of a human anti-TNFα antibody as presently claimed. Accordingly, Applicants respectfully request that the rejection of

the pending claims on the ground of nonstatutory obviousness-type double patenting, be reconsidered and withdrawn.

SUMMARY

In view of the foregoing, Applicants believe that the application is now in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicant's Attorney at (617) 449-6550

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Respectfully submitted,

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